

Application No. 10/549,893
Amendment dated: January 22, 2009

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REMARKS

Prior to this amendment, claims 1-6, 10 and 13-22 have been canceled without prejudice. Claims 7 - 9, 11, 12, 23-35 are pending. In this Amendment, claims 7 -22, 24 - 26 and 28 - 35 have been canceled without prejudice. Claims 23 and 27 have been amended. Support for these amendments can be found in the specification on page 64, line 25 through page 65, line 2. No new matter has been added by this amendment.

Applicants respectfully reserve the right to pursue any non-elected, canceled or otherwise unclaimed subject matter in one or more continuation, continuation-in-part, or divisional applications.

It is submitted that the claims, herewith and as originally presented were in full compliance with the requirements of 35 U.S.C. § 112. The amendment of the claims, as presented herein, is not made for purposes of patentability within the meaning of 35 U.S.C. §§ 101, 102, 103 or 112. Rather, this amendment is made simply for clarification and to round out the scope of protection to which Applicants are entitled. Furthermore, it is explicitly stated that the herewith amendment should not give rise to any estoppel.

Reconsideration and withdrawal of the rejections of this application in view of the amendments and remarks herewith, is respectfully requested, as the application is in condition for allowance.

1. Claims 7-9, 11-12 and 23-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tasaka et al. (WO 02/40484) in view of Dandiker et al. (US 5,425,950).

The Examiner States, "The claimed invention is a controlled release composition for oral administration, wherein

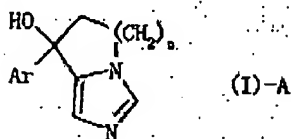
(A) a core containing

(1) a physiologically active substance which is a compound represented by the formula:

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where n is an integer of 1 to 3, and Ar is an aromatic ring which may be substituted, or a salt thereof, and

(2) hydrophilic polymers selected from hydroxypropylcellulose and low-substituted hydroxypropylcellulose, which is coated with

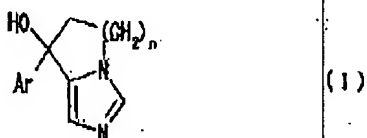
(B) a coating layer containing

(1) methacrylic acid copolymers as an enteric coating agent,

(2) talc as a lubricant, and

(3) a plasticizer selected from polyethylene glycol and triethyl citrate.

Tasaka teaches a compound of the formula:



wherein n is an integer of 1 to 3; and Ar is an optionally substituted aromatic ring, or a salt thereof (Page 4, lines 1-8). The compound (+)-6-(7-hydroxy-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-7-yl)-N-methyl-2-naphthamide is disclosed as one of the compounds (Page 6, lines 24-25). A pharmaceutical composition containing the compound, which is an antitumor agent, and which is an agent for the prophylaxis or treatment of breast cancer or prostate cancer is disclosed (Page 8, lines 6-14).

Pharmaceutically acceptable carriers that are used in the composition, including an excipient, a lubricant, a binder, a disintegrating agent and a thickener are disclosed (Page 39, lines 29-33). "Preferable examples of the excipient include lactose, sucrose, D-mannitol, starch, ... Preferable examples of the lubricant include magnesium stearate, calcium stearate, talc, colloidal silica ... Preferable examples of the binder include ... hydroxypropylcellulose, hydroxypropylmethylcellulose ... Preferable examples of the disintegrating agent include starch, carboxymethyl cellulose, carboxymethyl cellulose calcium, crosscarmellose sodium, sodium carboxymethyl starch ... Preferable examples of the thickener include natural gums ... Preferable examples of the solvent include ... propylene glycol ... Preferable examples of the dispersing agent include polyethylene glycol ... Preferable examples of the solubilizer include polyethylene glycol, propylene glycol ... Preferable examples of the isotonicity agent include ... glycerine ..." (Page 40, lines 4-33). The reference also discloses that a tablet, powder, granule or capsule can be prepared by adding "an excipient, a disintegrating agent, a binder, a

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lubricant and the like to the compound of the present invention, and subjecting the mixture to compression molding, and where necessary, coating for masking of taste, enteric coating or coating for sustention" (Page 41, lines 12-18). The pharmaceutical preparation can be administered orally (Page 42, lines 26-28) and a sustained release preparation can also be administered (Page 43, lines 8-9). Example 5 discloses the production of 6-(7-hydroxy- 6, 7-dihydro- 5H-pyrrolo [1,2-c] imidazol-7-yl)-N-methyl-2-naphthamide (Page 58, line 12 to Page 59, line 8).

Tasaka does not expressly teach methacrylic acid copolymers as enteric coating agents and a coating layer with a physiologically active substance.

Dandiker teaches tablet formulations where an enteric coating is applied by spraying a methacrylic acid copolymer containing solution (Col. 13, Example 9, lines 64-67). Dandiker also teaches a first active that is dispersed throughout a polymer matrix, and a second active that is dispersed throughout an excipient base. The mix with the second active "is compressed and the resulting tablets are further compression coated with the polymer matrix containing the first active" (Col. 13, Example 6, lines 12-25).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a composition comprising the compound of formula (I) and an enteric coating, as suggested by Tasaka, combine it with a methacrylic acid copolymer containing enteric coating, as taught by Dandiker, and produce the instant invention.

One of ordinary skill in the art would do this because methacrylic acid copolymers are known components of enteric coatings, as evidenced by the coating taught by Dandiker. One with ordinary skill in the art would know that the formulation taught by Tasaka can be enterically coated (Page 41, lines 12-18) and would use methacrylic acid copolymers for the enteric coating (as taught by Dandiker, (Col. 13, Example 9, lines 64-67) during the process of routine experimentation. One with ordinary skill in the art would have a reasonable expectation of success in producing a tablet with the compound of formula (1)-A that is enterically coated.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references. especially in the absence of evidence to the contrary.

Regarding instant claim 7, the controlled release composition is taught by the composition comprising the compound of formula (I) disclosed by Tasaka (Page 4, lines 1-8 and Page 43, lines 8-9). The physiologically active substance represented by the formula (1)-A would have been

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obvious over the compound of formula (I) taught by Tasaka (Page 4, lines 1-8 and Page 6, lines 24-25). The hydrophilic polymer would have been obvious over the hydroxypropylcellulose taught by Tasaka (Page 40, lines 8-10). The enteric coating would have been obvious over the enteric coating taught by Tasaka (Page 41, lines 12-18). The methacrylic acid copolymers for enteric coating would have been obvious over the enteric coating that is applied by spraying a methacrylic acid copolymer containing solution, as taught by Dandiker (Col. 13, Example 9, lines 64-67). The talc as lubricant would have been obvious over the talc taught by Tasaka (Page 40, lines 6-8). The plasticizer would have been obvious over the polyethylene glycol taught by Tasaka (Page 40, lines 4-33).

Regarding instant claims 8 and 32, the rapid release property of the physiologically active substance in the absence of the coating layer would have been obvious over the tablet without a coating layer as disclosed in Preparation Example 2 by Tasaka (Page 76, lines 12-23). A tablet without a coating layer will intrinsically have the property of rapid release of the active substance when compared to a tablet with a coating layer.

Regarding instant claim 9, the limitation of the core as a controlled release matrix would have been obvious over the controlled release hydrophilic polymer hydroxypropylcellulose taught by Tasaka (Page 40, lines 8-10).

Regarding instant claims 11-12 and 33, the pH dependent or delayed-dissolution type water solubility of the polymer in the coating layer and the insoluble or sparingly soluble polymer in the coating layer would have been obvious over the enteric coating of the composition taught by Tasaka (Page 41, lines 12-18) in view of the methacrylic acid copolymer used as an enteric coating agent, as taught by Dandiker (Col. 13, Example 9, lines 64-67). One with ordinary skill in the art would know that enteric coating polymers are water insoluble, pH dependent, and delay the dissolution of the active ingredient until after the acidic pH of the gastric passage.

Regarding instant claim 23, the compound would have been obvious over the (+)-6-(7-hydroxy-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-7-yl)-N-methyl-2-naphthamide taught by Tasaka (Page 6, lines 24-25). The hydrophilic polymer would have been obvious over the hydroxypropylcellulose taught by Tasaka (Page 40, lines 8-10). The enteric coating would have been obvious over the enteric coating taught by Tasaka (Page 41, lines 12-18). The methacrylic acid copolymers for enteric coating would have been obvious over the enteric coating that is applied by spraying a methacrylic acid copolymer containing solution, as taught by Dandiker (Col. 13, Example 9, lines 64-67). The talc as lubricant would have been obvious over the talc taught by Tasaka (Page 40, lines 6-8). The plasticizer would have been obvious over the polyethylene glycol taught by Tasaka (Page 40, lines 4-33).

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Regarding instant claim 24, the solubility of the physiologically active substance would have been obvious over the compound of formula (I) disclosed by Tasaka (Page 4, lines 1-8). The solubility of a compound is an intrinsic property of the compound and since the compound of formula (I) is taught by Tasaka, the solubility of the compound would be obvious over Tasaka.

Regarding instant claim 25, the limitation of the hydrophilic polymer used at about 3% to about 95% by weight would have been obvious over the hydrophilic polymers (hydroxypropylcellulose and hydroxypropylmethylcellulose) taught by Tasaka (Page 40, lines 8-10) and by the 70% w/w of hydroxypropyl methylcellulose (in the first polymer matrix) and 77% w/w of hydroxypropyl methylcellulose (in the second polymer matrix) as taught by Dandiker (Col. 13, Example 6, lines 12-25). One with ordinary skill in the art would find it obvious to use hydroxypropylcellulose or hydroxypropylmethylcellulose in the formulation since both are disclosed as applicable hydrophilic polymers by Tasaka.

Regarding instant claim 26, the controlled release composition coated with a coating layer which contains a physiologically active substance would have been obvious over the composition comprising the compound of formula (I) as taught by Tasaka (Page 4, lines 1-8 and Page 43, lines 8-9) in view of the coating with a different active as taught by Dandiker (Col. 13, Example 6, lines 12-25).

Regarding instant claims 27 and 34, the use of the controlled release composition for treating prostate cancer or breast cancer would have been obvious over the pharmaceutical composition used for the treatment of breast cancer or prostate cancer as taught by Tasaka (Page 8, lines 6-14). Moreover, the use of the controlled release composition for "prevention" of prostate cancer or breast cancer is an intended use and has no significance in composition claims.

Regarding instant claims 28-30, the limitation of a different release rate of a physiologically active substance would have been obvious over the composition with the compound taught by Tasaka (Page 4, lines 1-8 and Page 43, lines 8-9) in view of the pulsed release of the first active and sustained release of the second active taught by Dandiker (Col. 13, Example 6, lines 12-25).

Regarding instant claims 31 and 35, the dissolution characteristics of the controlled release composition would have been obvious over the composition comprising the compound of formula (I) and the sustained release preparation disclosed by Tasaka (Page 4, lines 1-8 and Page 43, lines 8-9). The dissolution characteristics of a composition are an intrinsic property of the composition and since a composition comprising the

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compound of formula (I) is taught by Tasaka, the dissolution characteristics of the composition would be obvious over Tasaka.”.

Applicants respectfully disagree. The amended claim 23 relates to the following controlled release composition having the improved sustainability of the effective blood concentration of the active substance.

A controlled release composition for oral administration, wherein

(A) a core containing (1) (+)-6-(7-hydroxy-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-7-yl)-N-methyl-2-naphthamide or a salt thereof, and (2) a hydrophilic polymer selected from hydroxypropylcellulose and low-substituted hydroxypropylcellulose, which is coated with

(B) a coating layer containing (1) methacrylic acid copolymers as an enteric coating agent, (2) talc as a lubricant, and (3) a plasticizer selected from polyethylene glycol and triethyl citrate,

wherein the core is in a granule form having the average particle diameter of from about 50 to about 2000 μm .

The above-mentioned amendments make it clear that the claimed composition is directed to a granular formulation wherein a core is coated with an enteric coating layer containing methacrylic acid copolymers as an enteric coating agent.

Meanwhile, Dandiker discloses tablets where an enteric coating is applied by spraying a methacrylic acid copolymer containing solution in Example 9 (column 13, lines 64-67).

However, an enteric coating containing a methacrylic acid copolymer, as taught by Dandiker, aims at not controlled release but targeting or delivery of drugs to the colon, as described in column 6, lines 36-44 which reads:

“When the pharmaceutical compositions of the invention (i.e. tablets) are provided with an enteric coating, this will delay the initiation of the erosion/disintegration of the underlying pH

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independent hydrophilic polymer layer until the tablet reaches a region of the gastrointestinal tract where a specific pH prevails.

Such enteric coated tablets allow targeting of drugs to the colon for either a direct local action, or to provide a preferred site for drug delivery."

Moreover, a tablet coated with an enteric coating layer containing methacrylic acid copolymer, as taught by Dandiker, cannot provide the effect of the claimed controlled release composition, as explained below.

A tablet having an enteric coating layer and a granular formulation having an enteric coating layer show the different variation of PK (pharmacokinetics) from each other.

Since a tablet usually contains all the necessary pharmaceutical ingredients in a single preparation, the gastric emptying of the ingredients is all or none. Therefore, in a tablet having an enteric coating layer, the variation of the gastric emptying time directly results in a change of time to let the physiologically active substance released in the intestine, which results in the considerable variability of PK.

It is an object of the controlled release to provide safe and efficient therapeutic agents showing stable PK by minimizing variability of PK which is caused by physiological factors. The tablet having an enteric coating layer cannot provide the aim due to the variability of the gastric emptying time.

To the contrary, in a granular formulation which can be administered in plural granules (for example, by capsule preparation), the granules stochastically (gradually) transfer from a stomach to an intestine, which is insusceptible to physiological factors.

Accordingly, the granular formulation such as the claimed composition, which can be administered as a unit (for example, capsule preparation) comprising plural granular substances coated with an enteric coating layer, is expected to show stable PK because of stable transfer to

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an intestine.

As explained above, a tablet having a general diameter (6mm-9mm) and a granular formulation have the different *in vivo* PK. This is also supported by the description of "Guideline for Bioequivalence Studies for Formulation Changes of Oral Solid Dosage Forms (2000)" issued by National Institute of Health Sciences (Japan), page 4, lines 10-11 which is attached as Exhibit A and reads:

"In the case of enteric coated products, the change in the size of the dosage form from less than 4 mm to more than 4 mm or vice versa is a formulation change of level E."

The claimed granular composition containing a pharmacologically-active compound, wherein a granule is coated with an enteric coating layer, is administered as the plural enteric granules, whereby stable kinetics of the gastric emptying can be provided. Therefore, the object of controlled release, namely safe and efficient therapeutic agents showing stable PK by minimizing variability of PK, which is caused by physiological factors, can be achieved.

Accordingly, we believe that the above-mentioned amendments can overcome the obviousness rejection under Tasaka et al. in view of Dandiker et al. Applicants respectfully request reconsideration.

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CONCLUSION

In view of the remarks made herein, the application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are respectfully requested. Please charge any required fee or credit any overpayment to Deposit Account No. 04-1105.

Dated: January 22, 2009

Respectfully submitted,

By


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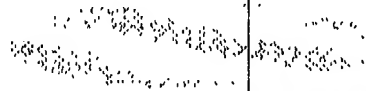
Attorneys/Agents For Applicant

Exhibit A

Guideline for Bioequivalence Studies for Formulation
Changes of Oral Solid Dosage Forms

February 14, 2000

経口固形製剤の処方変更の生物学的同
等性試験ガイドライン



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Appendix 3. Level of formulation change and tests

Section 1: Introduction

This guideline describes the principles of procedures of bioequivalence studies for post-approval change in the components and composition of oral solid dosage forms other than the active ingredients, which is hereafter called the formulation change. The objective of the study is to assure the bioequivalence between products before and after the formulation change. The tests required for bioequivalence assessment differ depending on the level of the change in formulation from the original product whose therapeutic efficacy and safety were established by clinical trials or whose bioequivalence was shown by human studies.

Section 2: Terminology

Original formulation: The formulation for which therapeutic efficacy and safety were established by clinical trials or bioequivalence was demonstrated by human studies.

Reference product: The product prior to formulation change which should be selected from among three marketed lots. The reference product should show intermediate dissolution among the three lots under the most discriminative condition, where the difference in dissolution between the fastest and slowest lots is the largest. The dissolution tests (Sec. 4) should be performed using 6 units, by the paddle method at 50 rpm.

Test product: Products after formulation change which should be manufactured in an production scale or 1/10 production scale or larger. The test product should be the same as the production lots in manufacturing method, quality and bioavailability. In the case of controlled release dosage forms test products should not significantly differ from the reference product in shape of dosage form, density and release mechanism. The dissolution characteristics of the test product should be similar to those of the reference product as required in the Guideline for Bioequivalence Studies of Generic products (Sec.3.B.1.2) published on December 22 in 1997 ([http://www.nihs.go.jp/drug/be-guide\(e\)/be97E.pdf](http://www.nihs.go.jp/drug/be-guide(e)/be97E.pdf)).

Products containing low solubility drugs: When the average dissolution from the reference product does not reach 85% in the testing time specified, that is, 2 hr at pH1.2 and 6 hr at other pHs (pH3.0-7.5), by the paddle method at 50 rpm without surfactants, they are defined as products containing low solubility drugs (see the Guideline for Bioequivalence Studies of Generic products (Sec.3.A.V.3.3)).

Section 3: Level of formulation change and test

1. Level of formulation change

First, levels of changes in individual excipients and categorized excipients, shown in Table 1 and Table 2, should be determined. If the change is equal to or less than the ranges of Level B, it is level B. If the change is more than the ranges of level B and equal to or less than the ranges of level C, it is level C. Similarly, the change in excipients in the range between C and D is level D. All changes exceeding the ranges of level D are level E. Any change in excipients whose use is limited to a trace belong to level A.

Among the above changes, the highest level of change is defined as the level of formulation change. In the case of enteric coated products, the change in the size of the dosage form from less than 4 mm to more than 4 mm or vice versa is a formulation change of level E.

Table 1. Level of Change in Individual and Categorized Excipients
(Uncoated Product)

Excipient Category and component	Level		
	B	C	D
Disintegrant			
Starch	3.0	6.0	9.0
Other	1.0	2.0	3.0
Binder	0.5	1.0	1.5
Lubricant or Polisher			
Ca or Mg stearate	0.25	0.50	0.75
Other	1.0	2.0	3.0
Glidant			
Talc	1.0	2.0	3.0
Other	0.10	0.20	0.30
Filler	5.0	10	15
Others ¹⁾	1.0	2.0	3.0
Total change ²⁾	5.0	10	15

Figures show the percent excipient (w/w) compared to total dosage form weight

1) e.g., preservatives, stabilizer. Excipients of trace use are excluded.

2) Total additive effects of all excipient changes

Table 2. Level of Change in Individual and Categorized Excipients
(Coated Product)

Core/ coated layer	Excipient Category and component	Level		
		B	C	D
Core	Disintegrant			
	Starch	3.0	6.0	9.0
	Other	1.0	2.0	3.0
	Binder	0.5	1.0	1.5
	Lubricant or Polisher			
	Ca or Mg stearate	0.25	0.50	0.75
	Other	1.0	2.0	3.0
	Glidant			
	Talc	1.0	2.0	3.0
	Other	0.10	0.20	0.30
	Filler	5.0	10	15
	Other ¹⁾	1.0	2.0	3.0
	Total change ²⁾	5.0	10	15
Film-coated layer ³⁾	Total change in components ^{2,4)}	5.0	10	15
	Weight of film coated layer/surface of core ⁵⁾	10.0	20	30
Sugar-coated layer	Total change in components ^{2,4)}	5.0	10	15
	Weight of sugar coated layer/surface of core ⁵⁾	10.0	20	30

Figures show percent excipient (w/w) compared to total dosage form weight.

1) e.g., preservatives, stabilizer. Excipients of trace use are excluded.

2) Total additive effects of all excipient changes

3) Except for sugar-coated layer, all film coated layers for water-proofing, undercoating, enteric coating and controlled release are included.

4) Excipients of trace use are excluded.

5) The surfaces of cores are determined from the shapes of dosage forms. If it is difficult, the surface should be calculated under the assumption that the cores are spheres and the densities do not change with the formulation change.

2. Tests

Level A

Dissolution tests should be performed using 12 units under the conditions specified in the registration or under the condition shown in Sec. 4 when the dissolution test is not specified. The equivalence in dissolution between test and reference products should be assessed according to the criteria described in Sec. 5 (1) and (2). There is no need for submission of the dissolution data which, however, have to be retained so as to be shown on demand.

Level B

Dissolution tests should be performed under the conditions shown in Sec. 4. Test and reference products are considered to be bioequivalent when their dissolution is judged to be equivalent according to the criteria in Sec. 5. If test and reference products are not equivalent in dissolution, bioequivalence tests should be performed according to the guideline for bioequivalence studies of generic products.

Level C

Conventional dosage forms and enteric coated products For products containing low solubility drugs, bioequivalence tests should be performed according to the guideline for bioequivalence studies of generic products. For other products, dissolution tests should be performed under the conditions shown in Sec. 4. Test and reference products are considered to be bioequivalent when their dissolution is equivalent according to the criteria in Sec. 5, except for narrow therapeutic range drugs listed in Table 3, For narrow therapeutic range drugs, test and reference products are considered to be bioequivalent if their average amounts dissolved at 30 min are equal to or more than 85% under all testing conditions and their dissolution is judged to be equivalent according to the criteria in Sec. 5. If test and reference products do not meet the requirement, bioequivalence tests should be performed according to the guideline for bioequivalence studies of generic products.

Controlled release dosage forms For products containing narrow therapeutic range drugs in Table 3, bioequivalence tests should be performed according to the guideline for bioequivalence studies of generic products. For other products, dissolution tests should be performed under the conditions shown in Sec. 4. Test and reference products are considered to be bioequivalent when their dissolution is equivalent according to the criteria in Sec. 5, If test and reference products are not equivalent in dissolution, bioequivalence tests should be performed according to the guideline for bioequivalence studies of generic products.

Table 3. Narrow Therapeutic Range Drugs¹⁾

Aprindine	Carbamazepine
Clindamycin	Clonazepam
Clonidine	Cyclosporine
Digitoxin	Digoxin
Disopyramide	Ethinyl Estradiol
Ethosuximide	Guanethidine
Isoprenaline	Lithium Carbonate
Methotrexate	Phenobarbital
Phenytoin	Prazosin
Primidone	Procaïnamide
Quinidine	Sulfonyleurea compounds ²⁾
Tacrolimus	Theophylline compounds ³⁾
Valproic Acid	Warfarin
Zonisamide	

1) Whether the drugs approved after 1999 belong to the narrow therapeutic category or not, should be determined referring to the above listed drugs.

2) Acetohexamide, glibenclamide, gliclazide, glycopyramide, tolazamide, tolbutamide

3) Aminophylline, choline theophylline, diprophylline, proxiphylline, theophylline

Level D

Conventional dosage forms For products containing low solubility drugs and narrow therapeutic range drugs, bioequivalence tests should be performed according to the guideline for bioequivalence studies of generic products. For other products, dissolution tests should be performed under the conditions shown in Sec. 4. Test and reference products are considered to be bioequivalent when their average amounts dissolved at 30 min are equal to or more than 85% under all testing conditions and their dissolution is judged to be equivalent according to the criteria in Sec. 5. If test and reference products do not meet the requirement, bioequivalence tests should be performed according to the guideline for bioequivalence studies of generic products.

Controlled release dosage form and enteric coated products Bioequivalence tests should be performed according to the guideline for bioequivalence studies of generic products.

Level E

Bioequivalence tests should be performed according to the guideline for bioequivalence studies of generic products.

Section 4. Dissolution test

Dissolution tests should be performed according to the conditions shown in Sec.3.A.V and Sec.3.B.I. When polysorbate 80 is added to test fluids for the dissolution tests of products containing low solubility drugs, the concentration should not exceed 0.1%. In the case of enteric coated products, the following test should be added to the dissolution tests specified in the guideline for bioequivalence studies of generic products (Sec.3.A.V);

Paddle method at 50 rpm in 900 ml of pH 6.0 buffer prepared with 0.01mol/L sodium monohydrogenphosphate and 0.005mol/L citric acid.

Section 5. Judgement of equivalence in dissolution

Test and reference products are considered equivalent when they meet both requirements (1) and (2) shown below. The rule is not applicable to conventional dosage forms and enteric coated products, unless the average dissolution from the reference product reaches 85% under any of the testing conditions within the testing time (2 hr at pH1.2 and 6 hr at other pHs) specified in Sec. 3.A.V.2 in the guideline for bioequivalence studies of generic products.

When similarity factor, f_2 is used, the dissolution data at the time points specified in Appendix 1 should be employed. If dissolution lag is observed for reference products, the equivalence in dissolution can be assessed using the dissolution profile normalized for the lag time. (see Appendix 2)

(1) Average dissolution

- 1) When the average dissolution from the reference product reaches 85% within 15 min: The average dissolution from the test product also reaches 85% within 15 min or does not deviate by more than 10% from that of the reference product at 15 min.
- 2) When the average dissolution from the reference product reaches 85% between 15 and 30 min: The average dissolution from the test product does not deviate by more than 10% from that of the reference product at two time points where the average amounts dissolved from the reference product are around 60 and 85%. When f_2 is used, the f_2 value should be not less than 50.
- 3) When the average dissolution from the reference product does not reach 85% in 30min: The following criteria should be applied to the comparison of average dissolution profiles determined in the testing times specified in Sec. 3.A.V.2 or Sec. 3.B.I.2 in the guideline for

bioequivalence studies of generic products (2 hr at pH1.2, 6 hr at other pHs for conventional and enteric coated products and 24 hrs for controlled release products). When the dissolution profiles are normalized for the lag time, the difference in average lag time between test and reference products should be not more than 10 min. The time points where the dissolutions are compared without use of f_2 , are the same as specified in the guideline for bioequivalence studies of generic products (Sec. 3.A.V.4).

- a. When the average dissolution from the reference product does not reach 50% at the testing time point: The average dissolution of test product does not deviate by more than 6 % from that of the reference product at the time points specified, or f_2 value is equal to or more than 60.
- b. When the average dissolution from the reference product is between 50 and 85 % at the testing time point: The average dissolution of test product does not deviate by more than 8 % from that of the reference product at the time points specified, or f_2 value is equal to or more than 55.
- c. When the average dissolution from the reference product reaches 85 % within the testing time: the average dissolution from test product does not deviate by more than 10 % from that of the reference product at the time points specified, or f_2 value is equal to or more than 50.

(2) Individual dissolution

Test products (n=12) should meet one of the following requirements at the final time points where the average dissolution is compared between test and reference products.

- a. When the average dissolution of reference product does not reach 50% within the testing time: There is no sample of test products that shows the deviation of more than 15% in dissolution from the average dissolution of the test product, and one or no sample that shows the deviation of more than 9 %.
- b. When the average dissolution of reference product is between 50 and 85 % at the testing time point: There is no sample of test product that shows a deviation of more than 20% in dissolution from the average dissolution of the test product, and one or no sample that shows a deviation of more than 12%.
- c. When the average dissolution of reference product reaches 85 % within the testing time: There is no sample of test product that shows a deviation of more than 25% in dissolution from the average dissolution of the test product, and one or no sample that shows a deviation of more than 15%.

Appendix 1.**f₂ (similarity factor) and time points****(1) Definition of f₂**

The following equation defines f₂, where T_i and R_i show the average percents dissolved from test and reference products at the time point (i), and n is the number of time points.

$$f_2 = 50 \log \left[\frac{100}{\sqrt{1 + \frac{\sum_{i=1}^n (T_i - R_i)^2}{n}}} \right]$$

(2) Time point for f₂

- 1) When the average dissolution from the reference product reaches 85% between 15 and 30 min: 15, 30, 45min.
- 2) When the average dissolution from the reference product reaches 85% between 30min and the testing time point*: Ta/4, 2Ta/4, 3Ta/4 and Ta where Ta is the time point at which average dissolution from the reference product reaches approximately 85%.
- 3) When the average dissolution from the reference product does not reach 85% at the testing time point*: Ta/4, 2Ta/4, 3Ta/4 and Ta where Ta is the time point at which average dissolution from the reference product reaches approximately 85% of the final amount dissolved in the testing time.

When there is a lag in dissolution, dissolution data normalized for the lag time should be used for the calculation of f₂.

* The testing time is specified in Sec. 3.A.V.2 or Sec. 3.B.I.2 in the guideline for bioequivalence studies of generic products.

Appendix 2.**Normalization of dissolution profiles with lag time**

The lag time is conventionally defined as the time when 5% of the drug dissolves. The lag time should be determined for individual dissolution by linear interpolation, followed by normalization of dissolution profiles for the lag time. Then, the average dissolution profiles are determined which can be used for the assessment of equivalence in average dissolution.

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Appendix 3.

Level of Formulation Change and Tests

Level	Dosage form ¹⁾	Therapeutic range	Solubility ²⁾	Dissolution	Test ³⁾
A	-	-	-	-	A single dissolution test
B	-	-	-	-	Multiple dissolution tests
C	IR, DR	Not narrow	Not low	-	Multiple dissolution tests
	"	"	Low	-	In vivo test
	"	Narrow	Not low	$\geq 85\%$, 30min	Multiple dissolution tests
	"	"	"	$<85\%$, 30min	In vivo test
	"	"	Low	-	In vivo test
	CR	Not narrow	-	-	Multiple dissolution tests
	"	Narrow	-	-	In vivo test
D	IR	Not narrow	Not low	$\geq 85\%$, 30min	Multiple dissolution tests
	Other IR, DR, CR	-	-	-	In vivo test
E	-	-	-	-	In vivo test

1) IR, DR and CR mean immediate release (conventional), delayed-release (enteric coated) and controlled release dosage forms, respectively.

2) Products containing low solubility drugs are determined by dissolution tests. When dissolution from the reference product does not reach 85% at 2 hr at pH1.2 and 6 hr at other pHs by paddle method at 50 rpm without surfactants, the drug is low solubility.

3) Single and multiple dissolution tests mean the test performed under specification conditions and those under multiple conditions. When equivalence in dissolution is not shown, in vivo tests should be performed according to the guideline for bioequivalence studies of generic products.

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